Remarks

By the foregoing amendment, claim 5 has been amended and claims 6-9 have been canceled. Support for the amendment to claim 5 can be found throughout the specification and specifically, for example, in the paragraph bridging pages 7 and 8. Applicants respectfully submit that no new matter has been added.

Telephone Interview with the Examiner

Applicants thank the Examiner for a telephone interview on February 4, 2008 with Applicants' representative, Thomas Weber. During the telephone interview, the Examiner confirmed that claim 6, and not claim 5, was intended to be rejected under 35 U.S.C. § 112. Therefore, Applicants address this rejection with respect to claim 6.

Response to the Office Action

Formal Matters

Applicants note with appreciation that the Office Action acknowledges the Claim of Priority under 35 U.S.C. § 119 and confirms that all copies of the certified copies of the priority document have been received by the Office.

Applicants also note with appreciation that the Action accepts of the drawings as submitted with the application.

Applicants thank the Examiner for considering the information submitted in the Information Disclosure Statement of December 12, 2006 by returning a signed and initialed copy of the Form PTO-1449.

Claim Objections

The Office Action objects to claims 5-9 for allegedly being improper under 37 C.F.R. 1.75. The Action asserts that claims 5 and 7 do not further limit the elements of claim 1 because the Examiner alleges that a CpG motif is inherently an active ingredient (claim 5) and an immunosuppressive agent (claim 7). As for claims 6, 8, and 9, the Examiner alleges that these claims contain recitations that are intended use.

By the foregoing amendment, Applicants respectfully request withdrawal of the objections to the claims. Claim 5 recites that the composition includes "at least one pharmaceutically acceptable excipient," thereby further limiting the recitations of parent claim 1. Furthermore, claims 6-9 have been canceled.

Claim Rejections under 35 U.S.C. § 112

The Office Action rejects claim 6 (as confirmed with the Examiner by telephone) under 35 U.S.C. § 112, first paragraph, for allegedly failing to enable for a pharmaceutical composition for preventing and or treating immune mediated diseases.

Withdrawal of this rejection is requested in view of the cancellation of claim 6.

Claim Rejections under 35 U.S.C. 35 U.S.C. § 103(a)

The Action rejects claims 1-9 under 35 U.S.C. § 103(a) as allegedly obvious over WO 98/1880 to Krieg et al. ("Krieg"). The Office asserts that Krieg discloses methylated oligonucleotides comprising a CpG motif. The Action also asserts that Krieg discloses a pharmaceutical composition comprising oligonucleotides as an immunosuppressive agent for preventing and/or treating immune-mediated diseases including arthritis.

Initially, prior addressing the merits of the rejections, Applicants submit the following.

As shown in Fig. 1A of the present application, mCG-DNA (CpG motifs comprising methylated cytosine) by itself can show weak immunostimulatory properties (IL-12 production-promoting property, see lane 4 from the top of Fig. 1A). However, CmG-DNA (CpG motifs comprising methylated guanine) do not show any immunostimulatory properties (as depicted in lane 5 from the top of Fig. 1A). It was demonstrated that immunostimulatory effects of unmethylated CpG can be significantly suppressed by CmG-DNA when compared relative to CG-DNA/mCG-DNA as opposed to mCG-DNA when compared relative to CG-DNA/CmG-DNA. This result is one of the features of the present invention. Also, mCG-DNA promotes immune activity in the presence of LPS (see LPS vs. LPS/mCG-DNA), while CmG-DNA does not show such immune activity promoting effect (see LPS vs. LPS/CmG-DNA). Similar results were obtained with respect to testing of IL-6 as disclosed in Fig. 1B. As a practical example,

Fig. 2 of the present application shows that CmG-DNA suppresses type II collagen arthritis in mice, thereby mirroring the results of Fig. 1 on an animal level.

In view of the foregoing points, Applicants submit that although the activities of CpG motifs comprising methylated cytosine have been described in Krieg (and also in Nature, vol. 374, 1995, pp. 546-549, which was cited in the Information Disclosure Statement), the studies of CpG comprising methylated guanines as described in the present application show unexpected results with respect to the immunosuppressive activities of these motifs.

Applicants also respectfully traverse this rejection on the following grounds. As a first point, Applicants respectfully submit that the Action only generally refers to Krieg and fails to pinpoint an anticipatory presence of each element of the examined claims. Furthermore, Applicants respectfully submit that Krieg fails to disclose a polynucleotide comprising any CpG motif wherein guanine is methylated, as required by claim 1.

As noted above, Krieg discloses some methylated DNA sequences but the methylations of Krieg's sequences are solely at the cytosine and not at the guanine. Furthermore, Applicants respectfully submit that there is no explanation in Krieg as to the differences between methylations of cytosine and guanine or advantages of methylated guanine over cytosine. In the absence of such explanation, one of ordinary skill in the art would not consider to investigate CpG motifs having methylated guanines. Therefore,

Applicants respectfully submit that one of ordinary skill in the art would not be motivated to arrive at the presently claimed invention by solely relying on Krieg.

The Office Action asserts that Krieg teaches "a pharmaceutical composition which is an immunosuppressive agent, wherein the agent is an agent for treating arthritis." Applicants respectfully traverse this allegation. Applicants submit that the agents disclosed in Krieg show immunostimulatory properties (see Krieg, e.g., Field of Invention, "The present invention relates to oligonucleotides and more specifically to oligonucleotides which have a sequence including at least one unmethylated CpG dinucleotide which are immunostimmulatory".). Furthermore, Krieg compares unmethylated CpG motifs with motifs comprising methylated cytosine (as opposed to the claimed methylated guanine). In the tests, the methylated CpG motifs do not show biological activities (see Krieg, pp. 45-46 and Table 9). Applicants submit that Krieg does not provide any further information regarding the biological activities, not to mention the immunosuppressive activities of the studied oligonucleotides. Without such information, one of ordinary skill in the art would not consider investigating the immunosuppressive properties of CpG motifs, more specifically CpG motifs that bear methylated guanines. Applicants respectfully submit that Krieg does not provide any motivation for using CpG motifs comprising methylated guanine as an immunosuppressive agent. Furthermore, Applicants submit that Krieg is silent with respect to the treatment of arthritis and thus does not disclose any pharmaceutical agents for treating arthritis.

The Action further asserts that Krieg teaches "an agent for suppressing generation of interleukin which comprising an oligonucleotide (polynucleotide) as an active ingredient." Applicants respectfully traverse this allegation as well. Applicants submit that Krieg fails to teach any suppression of the generation of interleukins but instead discloses the stimulation of interleukin formation (see Krieg, Figs. 13 and 14). Therefore, and in view of the above remarks regarding immunostimulatory results of Krieg, this document, at best, teaches away from the presently claimed invention.

Conclusion

In view of the foregoing, the Examiner is respectfully requested to reconsider and withdraw the rejections of record, and allow all the pending claims. Applicants respectfully submit that the Action has not established a *prima facie* case of obviousness in the rejections of claims 1-9. Furthermore, even if the Action would have established a case of obviousness, Applicants respectfully submit that such action is overcome by unexpected results observed with the present invention.

Should there be any questions, the Examiner is invited to contact the undersigned at the below listed telephone number.

Respectfully submitted,
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